

Salivary lactate dehydrogenase as a biomarker for squamous cell carcinoma

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Abstract

Oral cancer presents challenging and unresolved problems for the human population, and for a high-risk region like India it is of prime concern.

Considering the ever increasing incidence of oral carcinoma in India and worldwide, there is always a need to find out and standardize easier methods for screening, diagnostic as well as therapeutic purposes. In this view, the biochemical studies could prove to be promising in the future. Biochemical studies in the evaluation of cancers have shown that various substances alter quantitatively in the serum during tumor development.

The enzyme LDH is found in the cells of almost all body tissues. It is especially concentrated in the heart, liver, red blood cells, kidneys, muscles, brain, and lungs. Increased serum LDH activity is considered as a marker of cellular necrosis, and serum LDH levels have been used as a biochemical marker in the diagnosis of various cancers such as oral, laryngeal and breast cancer. LDH activity is mainly due to genomic changes during malignant transformation. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumor cells due to breakdown of glycoprotein.

Keywords: Lactate dehydrogenase, Oral squamous cell carcinoma, Serum, Nicotinamide-adenine dinucleotide.

Introduction

Cancer is one of the leading causes of adult deaths worldwide. Oral cancer is a serious problem in many countries. It accounts for significant mortality and is also responsible for extensive disfigurement, loss of function, behavioral changes, financial and sociologic hardship.⁽¹⁾ In the oral cavity, various tumor markers have been studied: These include oncofetal protein, (α -fetoprotein: Carcinoembryonic antigen), β -2 microglobulin and enzymes (lactate dehydrogenase [LDH]). One such marker is serum LDH.⁽²⁾

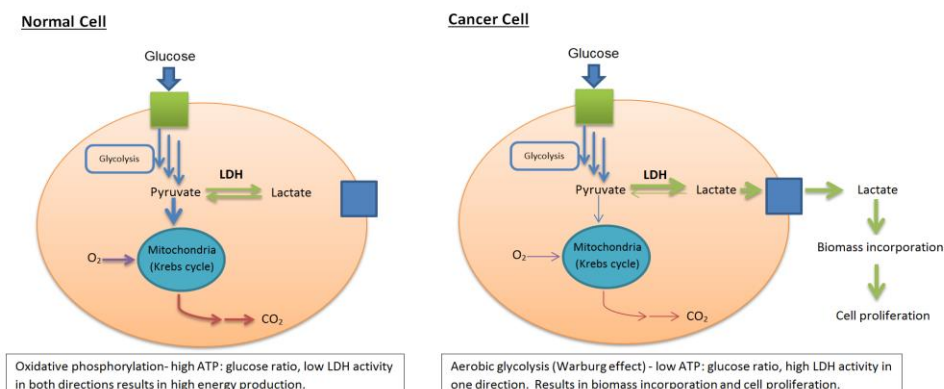
The enzyme Lactate Dehydrogenase (LDH) is an ubiquitous enzyme that was discovered in early periods of enzymology. This enzyme catalyzes the reaction of lactate production via pyruvate reduction during

anaerobic glycolysis. This enzyme is present in mostly all body tissues but mainly concentrated in heart, liver, red blood cells, kidneys, muscles, brains and lungs.⁽³⁾

In India, where the habits of chewing tobacco with betel nut, reverse smoking and heavy alcohol usage are common, there is a striking incidence of oral cancer, which accounts for as many as 30-40% of all cancers. About 90% of oral cancers are squamous cell carcinomas (OSCCs).⁽⁴⁾

Considering the ever increasing incidence of OSCC in India and worldwide, there is always a need to find out and standardize easier methods for screening, diagnostic as well as therapeutic purposes. In this view, the biochemical studies could prove to be promising in the future.

Biochemistry and physiology of LDH lactate dehydrogenase

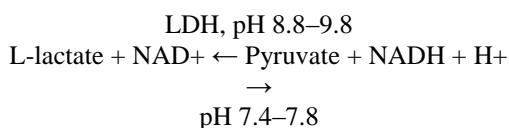


Source: LDH wikipedia, encyclopedia. Available as <http://en.m.wikipedia.org>

LDH is a hydrogen transfer enzyme that catalyses the oxidation of L-lactate to pyruvate with nicotinamide-adenine dinucleotide (NAD)⁺ as

hydrogen acceptor, the final step in the metabolic chain of anaerobic glycolysis. The reaction is reversible and the reaction equilibrium strongly favours the reverse

reaction, namely the reduction of pyruvate (P) to lactate (L):



LDH is an enzyme that catalyzes the reaction of lactate production via pyruvate reduction during anaerobic glycolysis. LDH is an enzyme detectable in the cytoplasm of almost every cell in the human body, which becomes extracellular upon cell death. Therefore, its extracellular presence is always related to cell necrosis and tissue breakdown.⁽⁵⁾

The three possible mechanisms responsible for the rise in the level of serum LDH in malignant subjects are: 1) Necrosis and cellular degeneration, 2) Induction process initiated by the tumor and involving normal tissue, 3) Muscle degeneration caused by protein deficit.⁽⁶⁾ Cancer cells preferentially utilize glycolysis instead of mitochondrial oxidative phosphorylation even in the presence of oxygen; this phenomenon is known as the Warburg effect.⁽²⁾

Types of LDH Isozymes

The enzyme is composed of four peptide chains of two types: M (muscle) and H (heart), each under separate genetic control.⁽⁷⁾ Heart (H) subunit or muscle (M) subunit are so named because of their predominance in the respective tissues. The enzyme is having five different isoenzymes, having different chemical and physical properties can be found. The isoenzymes all catalyse the same biochemical reaction but differ in their molecular structure, and are more or less organ specific. Therefore, isoenzyme patterns can be used to localize the source of LDH release. The isoenzymes differ in reactivity to substrates, sensitivity to inhibitors, resistance to heat inactivation, cold lability, and electrophoretic mobility in tertiary structure and charge. Therefore, isoenzymes are separable electrophoretically. The subunit compositions of the five isoenzymes in order of decreasing anodal mobility in an alkaline medium are: LDH-1 (HHHH; H4); LDH-2 (HHHM; H3M); LDH-3 (HHMM; H2M2); LDH-4 (HM3); and LDH-5 (MMMM; M4).⁽⁵⁾

Different LDH isoenzymes are found in different body tissues. The areas of highest concentration for each type of isoenzyme are:

1. LDH-1: heart and red blood cells
2. LDH-2: white blood cells
3. LDH-3: lungs
4. LDH-4: kidneys, placenta, and pancreas
5. LDH-5: liver and skeletal muscle

High levels of LDH indicate some form of tissue damage. High levels of more than one isoenzyme may indicate more than one cause of tissue damage. For example, a patient with pneumonia could also have a

heart attack. High levels of all five LDH isoenzymes could indicate multiple organ failure because LDH is in so many tissues throughout the body, complete LDH levels alone won't be enough to determine the location and cause of your tissue damage.⁽⁷⁾

A diagnosis will also require measuring the levels of LDH isoenzymes. For example, high LDH-4 and LDH-5 may mean either liver damage or muscle damage, but liver disease can't be confirmed without a full liver panel.

It's normal for a person to have a higher level of LDH-2 than LDH-1. After a heart attack, however, the level of LDH-1 rises and is usually higher than the level of LDH-2. This is called a flipped pattern.⁽⁸⁾

Significance

- i. Blood has been the media of choice for the study of the biochemical markers.
- ii. Increased serum lactate dehydrogenase (LDH) activity is considered as a marker of cellular necrosis and has been used as a biochemical marker in diagnosis of various cancers.
- iii. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumour cells due to breakdown of glycoprotein.^{9,10}

Applications

- i. As a general indicator of the existence and severity of acute or chronic tissue damage.
- ii. To detect and monitor progressive conditions such as anemia including hemolytic anemia and megaloblastic anemia, or severe infections.
- iii. To help stage, determine prognosis, and/or monitor treatment (i.e., chemotherapy) of cancers.⁽¹¹⁾

Laboratory procedure

Measurements of serum LDH

All blood samples were obtained through venous puncture before radical treatment. Levels of S-LDH were assayed based on an enzyme kinetics kit (Beijing Strong Biotechnologies, Beijing, People's Republic of China), according to the manufacturer's instructions. Measurements were carried out on a 7170A automated analyzer (Hitachi Ltd, Tokyo, Japan). The manufacturer-specified normal range of S-LDH using this kit is 135–225 U/L.⁽¹¹⁾

Condition associated with increase LDH level

LDH activity is mainly due to genomic changes during malignant transformation. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumor cells due to breakdown of glycoprotein. Increased LDH activity is considered as a marker of cellular necrosis.

- i. blood flow deficiency
- ii. cerebrovascular accident, such as a stroke
- iii. cancers
- iv. heart attack
- v. hemolytic anemia
- vi. infectious mononucleosis
- vii. liver disease, such as hepatitis
- viii. low blood pressure
- ix. muscle injury
- x. muscular dystrophy
- xi. pancreatitis
- xii. tissue death
- xiii. use of alcohol or certain drugs
- xiv. periodontal diseases⁽⁷⁾

Condition associated with lower LDH level

LDH deficiency affects how the body breaks down sugar for use as energy in cells, particularly muscle cells. It's very rare for a person to have low LDH levels.

Two types of genetic mutations cause low LDH level: LDH-A & LDH-B

- i. Lactate dehydrogenase A deficiency - It deficiency leads to fatigue, muscle pain and cramps during exercise (exercise intolerance), In some people high intensity exercise or strenuous activity leads to the breakdown of muscle tissue (rhabdomyolysis). The destruction of muscle tissue releases a protein called myoglobin which is processed by the kidneys and released in the urine (myoglobinuria) in some cases this can also leads to kidney failure.
- ii. Lactate dehydrogenase B deficiency - Affected individuals are usually discovered only when routine blood test reveal reduced LDH activity.
- iii. Ingestion of higher amount of ascorbic acid (vitamin C)^(7,12)

Conclusion

- i. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumor cells due to breakdown of glycoprotein.
- ii. The progressively increasing serum LDH level is positively correlated with the degree of cellular atypia suggesting that serum LDH level can serve as a biochemical tool in assessing the malignant potential of premalignant lesion.
- iii. Its alteration in histological tumour differentiation can be an indicator for the treatment and prognosis of oral cancer.
- iv. Serum LDH estimation can prove to be a valuable tool as a biochemical marker as it is a simple, non-invasive procedure and is easily accepted by the patient. Hence, LDH can be used as a diagnostic tool for early detection of cancer.

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